March 8, 2005

Ralph Parod, Ph.D., DABT
BASF Corporation
1609 Biddle Avenue
Wyandotte, MI 48192

Dear Dr. Parod:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Oxidized Cyclohexane, aq. Ext., posted on the ChemRTK HPV Challenge Program Web site on February 27, 2004. I commend BASF Corporation for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that BASF advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Acting Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/S/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Aqueous Extract of Oxidized Cyclohexane

Summary of EPA Comments

The sponsor, BASF Corporation, submitted a test plan and robust summaries to EPA for cyclohexane, oxidized, aqueous extract (EP-306 acid water; CAS No. 68915-38-8) dated December 30, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 27, 2004. The substance is a mixture that contains monocarboxylic acids, dicarboxylic acids, 6-hydroxycaproic acid, esters of alcoholic and acidic components, and trace amounts of oxidized cyclohexane.

EPA has reviewed this submission and has reached the following conclusions:

1. General Approach. The test plan contained inadequate information to support the proposed use of data on other substances to represent the toxicity of 6-hydroxycaproic acid and other components.

2. Physicochemical Properties and Environmental Fate. The data are adequate for these endpoints for the purposes of the HPV Challenge Program. For the biodegradation endpoint, the submitter needs to describe the calculation of the theoretical CO_2 evolution for the mixture.

3. Health Effects. Adequate data are available for the acute toxicity and gene mutation endpoints for the purposes of the HPV Challenge Program. The data provided for the repeated-dose, chromosomal aberration, reproductive, and developmental toxicity endpoints are inadequate; additional testing is needed to address these endpoints. In addition, the submitter needs to address deficiencies in the robust summaries.

4. Ecological Effects. EPA agrees with the submitter that adequate data are available for the fish endpoint. EPA reserves judgement on the adequacy of the aqueous invertebrate data pending receipt of missing data elements in the robust summaries. EPA disagrees with the submitter that adequate data are available for the algal endpoint; the submitter needs to provide adequate test data on EP-306 acid water.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Aqueous Extract of Oxidized Cyclohexane
Challenge Submission

General

The submitter provided data on individual components of EP-306 acid water mixture, adipic acid, and a C4 to C6 dicarboxylic acid mixture to address some of the SIDS endpoints. The test plan indicates that data on adipic acid are adequate to satisfy these toxicity endpoints because it is the major component of the submitted substance, EP-306 acid water. The test plan also indicates that 6-hydroxycaproic acid, the second most prevalent component of EP-306 acid water, is metabolically converted to adipic acid once absorbed into the body, and implies that a majority of the unidentified esters are also expected to be metabolized to adipic acid. The test plan asserts that adipic acid would thus be expected to comprise approximately 90% of the organic components in EP-306 acid water after metabolism and would also be expected to represent the toxicity of EP-306 acid water. However, 1) no supporting evidence was provided in the test plan to indicate that either 6-hydroxycaproic acid or the unidentified esters are metabolically converted to adipic acid and no discussion was provided for the rate or extent of metabolic conversion to adipic acid or formation of other potential metabolites; 2) even if such data were provided,

data on a subset of components of a mixture are not always appropriate for assessing its potential health and environmental effects. In this case, data were provided only on dicarboxylic acids, which may not adequately characterize the potential toxicity of the short-chain mono-carboxylic acids, esters or other components that constitute up to ~30% of EP-306's organic components.

Therefore, data on the selected individual components of EP-306 acid water are not adequate for the purposes of the HPV Challenge Program. Additional test data on EP-306 acid water are needed to address its toxicity.

The Test Plan refers several times to EP-306 as "site-limited." However, the test plan does not include a formal, supported claim of closed system intermediate status.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data are adequate for these endpoints for the purposes of the HPV Challenge Program. Additional information about the nature of the 5-10% of "other" components ("primarily esters of 6-hydroxycaproic acid and acidic components") would be helpful in further assessment of the substance.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data are adequate for photodegradation, stability in water, biodegradation, and fugacity for the purposes of the HPV Challenge Program. However, for the biodegradation endpoint, the sponsor needs to describe calculation of the theoretical CO_2 evolution for the mixture. For stability in water, the technical discussion in the test plan also needs to appear as a robust summary.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for the acute toxicity and gene mutation endpoints for the purposes of the HPV Challenge Program. The data provided on components of the mixture are inadequate to characterize the repeated-dose, chromosomal aberration, reproductive, and developmental toxicity endpoints for reasons discussed in the "General" section. The submitter needs to provide an *in vitro* chromosomal aberration assay and a combined repeated-dose/reproductive/developmental toxicity screening test on the mixture following OECD TGs 473 and 422, respectively. In addition, the submitter needs to address deficiencies in the robust summaries.

Ecological Effects (fish, invertebrates, and algae)

Fish. The data provided for the fish endpoint are based on a 96-hour study in *Leuciscus idus* (golden orfe), using EP-306 acid water. Because no mortality occurred at concentrations up to 1000 mg/L at neutral pH, these data are adequate even though the study was conducted in a species that is not recommended by OECD Guideline 203. The submitter needs to revise the robust summary to provide missing study details (see Specific Comments on Robust Summaries).

Invertebrates. EPA reserves judgement on the adequacy of the *Daphnia* study pending receipt of a revised robust summary providing missing study details and adequate discussion and resolution of the inconsistencies in the analytical monitoring results (see Specific Comments on Robust Summaries).

Algae. No data were submitted for the toxicity of *algae* on EP-306 acid water. Data on adipic acid and on C4-C6 dicarboxylic acid mixture were submitted to address the algal toxicity endpoint without supporting robust summaries. In addition, as previously discussed, the data on selected individual

components are not adequate to characterize the toxicity of the mixture in this case. Testing (OECD TG 201) is needed to address this endpoint.

Specific Comments on the Robust Summaries

Health Effects

Acute toxicity. Missing study details included the year of the study and test substance identity and purity.

Genetic toxicity. Missing study details included the year of the study, identification of the test substance, purity of the test substance, incubation conditions, number of colonies counted, response to positive controls, and the criteria for evaluating results.

Ecological Effects

Fish. Missing study details included characterization of the test substance, loading rate of the fish, and statistical methods used. In addition, analytical monitoring was not performed. The LC_{50} was reported as a concentration range; OECD TG 203 stipulates the reporting of a discrete LC_{50} value with 95 percent confidence limits.

Aquatic invertebrates. Missing study details included characterization of the test substance. The robust summary reported that test material recovery ranged from 100% to 150%, which was based on the 6-hydroxyhexanoic acid component. If 6-hydroxyhexanoic acid esters in the mixture form the acid under the test conditions, then analytical monitoring based on 6-hydroxyhexanoic acid may be problematic. The submitter needs to provide an explanation of the 150% recovery and adequate discussion and resolution of the analytical monitoring results in addition to an adequate identification and characterization of the test substance in a revised robust summary.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.